-continued

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Thr Thr Ile Ala Gly Val Val Tyr Lys Asp Gly Ile Val Leu Gly Ala
1 5 10 15

Asp Thr Arg

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: Not Relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Xaa Xaa Ile Ala Gly Val Val Tyr Lys Asp Gly Ile Val Leu Gly Ala
1 5 10 15

Asp Thr Arg

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: Not Relevant
(D) TOPOLOGY: linear

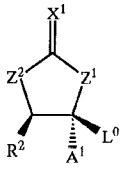
(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Thr Thr Ile Ala Gly Val Val Tyr Lys
1 5

What is claimed is:

1. A pharmaceutical composition comprising a compound having the following formula



wherein Z^1 is O, S, SO_2, NH, or NR_a, R_a, being C_{1-6} alkyl;

X^1 is O, S, CH_2, two singly bonded H, $CH(R_b)$ in the E or Z configuration, or $C(R_b)$ (R_c) in the E or Z configuration, each of R_b and R_c, independently, being C_{1-6} alkyl, C_{6-12} aryl, C_{3-8} cycloalkyl, C_{3-8} heteroaryl, C_{3-8} heterocyclic radical, or halogen, X^1 being two singly bonded H when Z^1 is SO_2;

Z^2 is O, S, NH, NR_d, CHR^1, or $CHOR^1$ in the (R) or (S) configuration, wherein R_d is C_{1-6} alkyl and R^1 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, NR_dR_e (except where Z^2 is $CHOR^1$), or the side chain of a naturally occurring α-amino acid, or R^1 and R^2 taken together are a bivalent moiety, provided that when R^1 and R^2 are taken together, Z^1 is NH or NR_a and Z^2 is CHR^1; R_e being H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and the bivalent moiety forming a C_{3-8} cycloalkyl, C_{3-8} heteroaryl, C_{3-8} heterocyclic radical, or C_{6-12} aryl, where the H in CHR^1 is deleted when R_1 and R_2 taken together form a C_{3-8} heteroaryl or C_{6-12} aryl;

R^2 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, azido, C_{2-6} alkynyl, halogen, OR_f SR_f, NR_fR_g, $—ONR_fR_g$, $—NR_g(OR_f)$, or $—NR_g(SR_f)$ (each of R_f and R_g, independently, being H, C_{1-6}, alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), or R^1 and R^2 taken together are a bivalent moiety, the bivalent moiety forming a C_{3-8}cycloalkyl, C_{3-8} heteroaryl, C_{3-8} heterocyclic radical, or C_{6-12} aryl, where the H in CHR^1 is deleted when R_1 and R_2 taken together form a C_{3-8} heteroaryl or C_{6-12} aryl;

A^1 is H, the side chain of any naturally occurring α-amino acid, or is of the following formula,

$$—(CH_2)_m—Y—(CH_2)_n—R^3X^3$$

wherein Y is O, S, C=O, C=S, —(CH=CH)—, vinylidene, $—C=NOR_h$, $—C=NNR_iR_i$,, sulfonyl, methylene, CHX^4 in the (R) or (S) configuration, or deleted, X^4 being halogen, methyl, halomethyl, OR_h, SR_h, NR_iR_i, $—NR_i(OR_h)$, or $—NR_i(NR_iR_i)$, wherein R_h is selected from

-continued

/ note="SELECTED FROM: Nle, Leu, Phe, Val, Mox(methoxinine), naphthyAla or a hydrophobic, substituted aromatic amino acid or aralkylamine or is deleted."

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Xaa Xaa Trp Xaa Xaa Xaa Xaa Xaa Xaa
1 5

We claim:

1. A compound of formula (I)

$XX^1TrpX^2X^3X^4X^5X^6X^7NH_2$ (I) (SEQ ID NO: 3)

wherein

X is a group X^8Arg or D-Arg X^9X^{10}

and X^8 is des NH_2Pro,TyrPro,des NH_2TyrPro, Ada, Pro, D-Pro or is deleted;

X^9 is Gly, Ala, D-Ala or is deleted;

X^{10} is Asn, Phe, D-Phe, or Phe or D-Phe substituted by one or more halo atoms;

or X is a group A—(CH_2)n—CO— in which A is a group containing 1 to 3 rings of which at least one ring is aromatic, each ring system being optionally substituted; and the alkylene group is optionally substituted by one to four groups selected from amino, hydroxy C_{1-4} alkoxy and C_{1-4} alkyl optionally substituted by halo and n is 0 to 4,

or X is a group A—(CH_2)n—CO— in which A is an optionally substituted aromatic residue containing 1 to 3 rings and the alkylene group is optionally substituted by one to four groups selected from amino, C_{1-4} alkoxy and C_{1-4} alkyl optionally substituted by halo and n is 1 to 4,

or X is cyclopentylcarbonyl substituted by a group X^8 Arg (or D-Arg) X^9 X^{10} as hereinbefore defined;

X^1 is His, ThiAla or is deleted;

X^2 is Ala, D-Ala, CPenc, D-tBuGly or Pro;

X^3 is Val or Val substituted by one or more halo atoms;

X^4 is Gly, Ala, D-Ala, Sarcosine, Pro, D-Pro or D-Phe;

X^5 is His or ThiAla;

X^6 is D-Proψ, Proψ, 2-pyrrolidinyl-3-hydroxypropionyl or D-Pro; and

X^7 is Nle,Leu,Phe,Val,Mox, D-Phe or Phe, or D-Phe substituted by one or more halo atoms or naphthylAla or naphthyl D-Ala or a hydrophobic, substituted aromatic amino acid or aralkylamine or is deleted;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein X is a group A—$(CH_2)_n$—CO— in which A is phenyl, naphthyl, phenothiazinyl or indolyl optionally substituted by hydroxy, phenyl, halo, C_{1-4} alkyl or C_{1-4} alkoxy optionally substituted by halo; and n is 2.

3. The compound of claim 2 whercin A is phenyl or naphthyl optionally substituted by hydroxy, phenyl, halo, C_{1-4} alkyl or C_{1-4} alkoxy optionally substituted by halo; and n is 2.

4. The compound of claim 1 wherein X^8 is des NH_2TyrPro or des NH_2Pro; X^9 is Gly or D-Ala; X^{10} is D-Phe; and n is 2.

5. The compound of claim 1 wherein said compound of formula (I) is

N-((R)-2-(6-Methoxy-2-Naphthyl)Propionyl)-HisTrpAlaValD-AlaHisD-ProψNle-NH_2;

N-((S)-2-(6-Methoxy-2-Naphthyl)Propionyl)-HisTrpAlaValD-AlaHisD-ProψNle-NH_2;

N-((S)-3-Phenylbutyryl)-HisTrpAlaValD-AlaHis D-ProψNle-NH_2;

N-((R)-3-Phenylbutyryl)-HisTrpAlaValD-AlaHis D-ProψNle-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaVal D-Ala(3-(2-Thi)-Ala)D-ProψNle-NH^2;

N-((S)-3,3,3-Trifluoro-2-Methoxy-2-Phenyl-Propionyl)-HisTrpAlaValD-ProψNle-NH^2;

N-((R)-3,3,3-Trifluoro-2-Methoxy-2-Phenyl-Propionyl)-HisTrpAlaValD-ProψNle-NH_2;

N-3-(((4'-Hydroxy)Phenyl)Propionyl)-ProD-ArgGly D-PheHisTrpAlaValGly-HisD-ProψNle-NH_2;

N-(((4'Hydroxy)-3-Phenyl)Propionyl)-Pro D-ArgHisTrpAlaValD-AlaHisD-ProLeu-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-AlaHis D-Proψmox-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-ProψPhe-NH_2;

N-((3-Phenyl)Propionyl)-TrpAlaValD-AlaHis D-ProψLeu-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpProValD-ProHis D-ProψLeu-NH_2;

N-3-(((3'-Trifluoromethyl)Phenyl)Propionyl)-HisTrpAlaValD-AlaHisD-ProψLeu-NH_2;

N-((3-Phenyl)Propionyl)-(3-(2-Thi)-Ala)TrpAlaVal D-AlaHisD-ProψLeu-NH_2;

N-((deamino-Pro)-D-ArgD-Ala D-PheHisTrpAlaValGlyHisD-ProψNle-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValGlyHis D-ProψNle-NH_2;

N-((deamino-Pro)-D-ArgD-AlaD-PheHisTrpAlaVal D-AlaHisD-ProψNle-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-AlaHis D-ProψNle-NH_2;

TyrProD-ArgGlyD-PheHisTrpAlaValGlyHis D-ProψNle-NH_2;

D-ArgGlyD-PheHisTrpAlaValGlyHisD-ProψNle-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-AlaHis D-ProPhe-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-AlaHis D-Proψ(3-(2-Naphthyl)-D-Ala)-NH_2;

N-((3-Phenyl)Propionyl)-HisTrpAlaValD-PheHis D-ProψPhe-NH_2;

D-PheHisTrpAlaValD-AlaHisD-ProψPhe-NH_2;

N-((3-Phenyl)Propionyl)-D-ProArgGly D-PheHisTrpAlaValD-AlaHisD-ProψPhe-NH_2;

N-((3-Phenyl)Propionyl)-(3-(2-Thi)-Ala)-TrpAlaVal D-AlaHisD-ProψPhe-NH_2;

Typically the compounds described above are formulatedinto pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance inthese compositions or preparations is such that a suitable dosage in the range indicated is obtained.

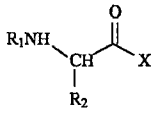
Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; adisintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint,oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance,tablets may be coated with shellac, sugar or both. A syrupor elixer may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc. or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or cus-tomary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

We claim:

1. A compound of the formula



the hydrates thereof, and the pharmaceutically acceptable salts thereof useful for inhibiting human leukocyte elastase wherein

R_2 is the side chain of the α-amino acids Ala, Leu, Ile, Val, n-Val or n-Leu,

R_1 is $-P_2P_3P_4Pg$ with P_2 being Pro or Ala,

P_3 is Ala, Leu, Ile, Val, n-Val, n-Leu or Lys,

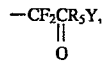
P_4 is Ala or is deleted,

P_g is an optional terminal moiety selected from Ac, Suc, Bz, Boc, CBZ, DNS, Iva, MeOSuc, $AdSO_2$, AcAc or 2-CBZ,

X is X_1 or X_2 wherein

X_1 is $-CF_3$, $-CF_2H$, $-CO2R_3$ or $-CONHR_3$,

X2 is

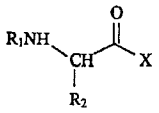


Y is $-OR_3$,

R_3 is hydrogen, C_{1-4} straight or branched alkyl, phenyl, benzyl, cyclohexyl or cyclohexylmethyl, and

R_5 is deleted, with the proviso that when the R_1 moiety bears a Pro in its P_2 position, then X is other than CF_3.

2. A compound of the formula



the hydrates thereof, and the pharmaceutically acceptable salts thereof useful for inhibiting Cathepsin G wherein X, X_1, X_2, R_3, R_5 and Y are as defined in claim **1**.

R_1 is $-P_2P_3P_4Pg$ with P_2 being selected from Pro or Ala or is selected from Ac, Suc, Bz, Boc, CBZ, DNS, Iva, MeOSuc, $AdSO_2$, AcAc or 2-CBZ when P_3, P_4 and P_g are deleted,

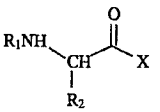
P_3 is Ala, Leu, Ile, Val, n-Val, n-Leu, Gly, or is deleted,

P_4 is Ala or is deleted,

P_g is selected from the group consisting of Ac, Suc, Bz, Boc, CBZ, DNS, Iva, MeOSuc, $AdSO_2$, AcAc or 2-CBZ or is deleted, and

R_2 is a side chain of an amino acid selected from Phe or Tyr.

3. A compound of the formula



the hydrates thereof, and the pharmaceutically acceptable salts thereof useful for inhibiting chymotrypsin wherein X, X_1, X_2, R_3, R_5 and Y are as defined in claim **1**,

R_1 is $-P_2P_3P_4Pg$ with P_2 being selected from Ala, Val or n-Val or is selected from Ac, Suc, Bz, Boc, CBZ, DNS, Iva, MeOSuc, $AdSO_2$, AcAc or 2-CBZ when P_3, P_4 and P_g are deleted,

P_3 is deleted,

P_4 is deleted,

P_g is selected from the group consisting of Ac, Suc, Bz, Boc, CBZ, DNS, Iva, MeOSuc, $AdSO_2$, AcAc or 2-CBZ or is deleted, and

R_2 is a side chain of an amino acid selected from Phe or Tyr.

4. A compound of claim **1** having one of the formulae
MeOSuc-Ala-Ile-Pro-Val-CO_2Me,
MeOSuc-Ala-Ile-Pro-Val-CF_2COOEt,
MeOSuc-Ala-Ile-Pro-Val-CHF_2,
MeOSuc-Ala-Ala-Pro-Val-CO_2Me,
Lys-Pro-Val-CHF_2,
Lys-Pro-Val-CO_2Me, and
MeOSuc-Ala-Ile-Pro-Val-CO_2H.

5. A compound of claim **2** having one of the formulae
Suc-Ala-Ala-Pro-Phe-COOH,
Suc-Ala-Ala-Pro-Phe-COOMe,
Suc-Ala-Ala-Pro-Phe-CF_2H, and